**Comments by the Center for Regulatory Effectiveness ("CRE") to Office of Management and Budget ("OMB") on "ICR Addendum for the Second List of Chemicals; Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP)" (EPA ICR No. 2488.01, OMB Control No. 2070—[new], http://www.gpo.gov/fdsys/pkg/FR-2013-06-14/pdf/2013-14233.pdf. Comments Filed June 15, 2013, in Docket EPA–HQ–OPPT–2013–0275, at www.regulations.gov ; and at *oira_submission@omb.eop.gov* to *OMB Desk Officer for EPA*.**

## I. Executive Summary

EPA has already required that one set of chemicals be tested by EPA's current EDSP Tier 1 battery of tests. On May 21-23, 2013, EPA's Science Advisory Panel ("SAP") peer reviewed data from this first set of chemicals. SAP review is required by statute.[1] EPA now wants to require that additional chemicals be tested by this same EDSP Tier1 test battery, even though the SAP described the entire battery Endocrine pathway performance as "relatively poor," and recommended against additional testing by one of the Tier 1 tests. For the following reasons, OMB/OIRA should not approve the ICR necessary for these additional EDSP Tier 1 tests.

- OMB/OIRA should not approve this ICR because it authorizes an EDSP Tier 1 test battery which includes the Amphibian Metamorphosis Assay ("AMA"). The SAP recommended that the AMA not be used for any additional tests because there were obvious and significant problems with the AMA test results for the first set of chemicals. In the SAP's own words, "[T]he Panel strongly feels that the issue of the bent tail in [Charge] Question 5 and thyroid histology in [Charge] Question 6 and their interaction with other endpoints associated with the AMA, leads to a recommendation that the Agency look at the change in the experimental design of the AMA ." Given these obvious problems with the AMA test data so far, the SAP stated its concerns about the "utility" of the test, and recommended that EPA not use the current test for substances in addition to those already tested.[2]

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[1] 21 USC § 346a(p)(2).

[2] Meeting Transcript, FIFRA SCIENTIFIC ADVISORY PANEL (SAP) OPEN MEETING, SCIENTIFIC REVIEW OF THE ENDOCRINE DISRUPTOR SCREENING PROGRAM (EDSP); TIER I SCREENING ASSAY AND BATTERY PERFORMANCE, DOCKET NUMBER: EPA-HQ-OPP-2013-0075, pages 428 and 433, at http://www.epa.gov/scipoly/sap/meetings/2013/may/052113transcript.pdf. EPA's Charge Questions to the SAP are available as Document ID: EPA-HQ-OPP-2013-0075-0005, at www.regulations.gov.

In EPA's own words, the "recommendations of the Panel from the May FIFRA SAP will be **critical** in how the Agency conducts its weight-of evidence (WoE) evaluation of the Tier 1screening results…."[3]

If OMB/OIRA approves this ICR, then they will enable EPA to ignore the SAP's unambiguous peer review recommendation that the AMA NOT BE USED for additional chemicals.

- OMB/OIRA should not approve an ICR for an EDSP Tier 1 test battery which does not contain the AMA. The EDSP Tier 1 test battery was designed to be conducted as a whole to determine the potential of a chemical to interact with the E, A, or T hormonal pathways. Each assay is critical to the utility of the entire battery as an endocrine disruptor screen. Consequently, loss of the AMA precludes utility for the rest of the battery. In EPA's own words, the AMA is an "essential" component of the EDSP Tier 1 test battery.[4]

- OMB/OIRA should not approve this ICR because, as a separate flaw with the battery as a whole and unrelated to the AMA problems, the SAP concluded that the Tier 1 test results so far "suggest that the complementary performance of the multiparameter E [endocrine] battery tests was relatively poor." [5]

- OMB/OIRA should not approve this ICR because--for the reasons stated above and discussed in more detail below--the EDSP Tier 1 test battery will not generate accurate, valid and reliable information that has utility.[6] Consequently, the EDSP Tier 1 test battery violates OMB/OIRA's and EPA's Information Quality Act ("IQA") guidelines.

- OMB/OIRA should not approve this ICR because the EDSP Tier 1 test battery violates the Paperwork Reduction Act ("PRA") and OMB/OIRA's practical utility rules. The PRA and OMB's rules require that EPA provide a record demonstrating that the EDSP Tier 1 tests have practical utility: *i.e.*, EPA has to show that these tests will generate accurate, valid, reliable and useful information.[7] For the reasons stated above

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[3] Pages 22875-76, at http://www.gpo.gov/fdsys/pkg/FR-2013-04-17/pdf/2013-08921.pdf (emphasis added).

[4] EPA White Paper for SAP review, page 12, Document EPA-HQ-OPP-2013-0075-0003 at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2013-0075-0003 .

[5] SAP Meeting Transcript, page 460, at http://www.epa.gov/scipoly/sap/meetings/2013/may/052113transcript.pdf .

[6] *E.g.*, Page 12 of OMB IQA Guidance at http://www.whitehouse.gov/sites/default/files/omb/inforeg/iqg_comments.pdf ; IQA guidelines, page 15 and Section 6.5, page 28 , available online at http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf ; OMB Government-wide IQA Guidelines, Section V.3, available online at http://www.whitehouse.gov/omb/fedreg_final_information_quality_guidelines .

[7] 5 CFR §§1320.3(l); 1320.5(d)(1)(iii); 5 CFR § 1320.5(e).

and discussed in more detail below, the EDSP Tier 1 test battery will not generate accurate, valid, reliable, and useful information.

- OMB/OIRA should not approve this ICR because EPA is abandoning the EDSP Tier 1 test battery covered by this ICR and replacing it with "faster and more cost effective test methods." Consequently, the EDSP Tier 1 test battery violates the PRA because it is for tests which are not the least burdensome necessary, and for tests which are not necessary for the proper performance of the functions of the Agency.[8]

## II. OMB/OIRA Should Not Approve an ICR for a Tier 1 Test Battery Which Includes the AMA Because the "Critical" SAP Recommended that EPA Not Use the AMA

EPA asks OMB/OIRA to approve a new ICR for additional EDSP Tier 1 testing using a test battery that includes the AMA. This EPA request flies in the face of an SAP recommendation that EPA not use the AMA for any additional tests. In the SAP's own words:

> "The Panel realizes that there is a very high instance, 83 percent of the studies that show this issue of bent tail or spinal curvature, and they do feel that this has potential of impacting the assay."
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> "The Panel feels that without an evaluation of the weight of evidence, the AMA must today be considered important as a Tier 1 screen. But the prevalence and variability and the percent of clutches expressing this general tail malformation or bent tail, does affect competence [sic] in the utility of the assay. The Panel further understands that the protocol represented the state of the science in 2008 when the initial Tier 1 testing order was issued. The Panel agrees with the Agency in not altering that protocol until the first round of testing was completed. While this SAP is based on only 21 of the chemicals being tested in this initial order, the Panel feels there is sufficient evidence with the AMA that the protocol be reevaluated as soon as possible. However, the Panel also recommends not changing the experimental design of the actual study outcomes until all 52 chemicals are evaluated. The reason for the discrepancy here, the Panel wasn't sure whether all 52 chemicals have been tested, and only 21 have been evaluated by the Agency or there are others that are in the process. We're not asking the Agency to change the horse in the middle of the stream, but as soon as you get to shallow water on the other side, start looking at another way to get across the river."
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[8] See 44 U.S.C. 3508, at http://www.law.cornell.edu/uscode/text/44/3508 ; 5 CFR 1320.5(d), at http://www.law.cornell.edu/cfr/text/5/1320.5 .

> "[T]he Panel feels the bent tail issue has the potential to impact both performance criteria for acceptance of NGO test results and scientific competence [sic] in the utility and the validity of the AMA. Therefore, the Panel recommends the Agency determine the cause and possible mode of action for the bent tail syndrome so guidance can be given to the laboratories in how to eliminate it or at least reduce its morbidity response to less than 10 percent of the population."
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> "[T]he Panel strongly feels that the issue of the bent tail in [Charge] Question 5 and thyroid histology in [Charge] Question 6 and their interaction with other endpoints associated with the AMA, leads to a recommendation that the Agency look at the change in the experimental design of the AMA study. It is further recommended that the Agency specifically look into the development of stage-dependent, rather than time-dependent protocol." [9]

CRE is not surprised by the SAP's conclusions and recommendations. In 2008, CRE filed a Request for Correction ("RFC") under the Information Quality Act ("IQA"). This RFC asked EPA to correct the Agency's publicly disseminated statements that the AMA had passed peer review and was properly validated. CRE's RFC pointed out that the AMA had received a negative peer review report and asked EPA not to use the AMA as part of the EDSP Tier 1 test battery.[10]

EPA used the AMA in the EDSP anyway.[11]

CRE's RFC pointed out that a 2007 peer review report which preceded SAP review of the AMA included the following criticisms of the test. For example, one peer reviewer explained that the inter-laboratory inconsistencies obvious in just one table of the AMA validation study "would convince any reviewer for a reputable scientific journal to recommend rejection" of the validation study. [12]

This peer reviewer further stated "that the conclusions regarding inter-laboratory variability are not warranted and that it [the AMA test protocol] fails as a method for

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[9] SAP Meeting Transcript, pages 426, 428, 429, and 433 at http://www.epa.gov/scipoly/sap/meetings/2013/may/052113transcript.pdf .
[10] CRE's AMA RFC is available online at http://www.epa.gov/QUALITY/informationguidelines/documents/08004.pdf .
[11] EPA's response to CRE's RFC is available online at http://www.epa.gov/QUALITY/informationguidelines/documents/08004-response.pdf .
[12] *Peer Review Results for the Amphibian Metamorphosis Assay* ("Peer Review Report"), page 3-7, available online at http://www.epa.gov/endo/pubs/ama_peer_review_121907.pdf .

accomplishing the stated goal of the assay to be part of the Endocrine Disruptor Screening program (EDSP)."[13]

He advised EPA that "[b]efore the AMA can be used as a screening tool that is open to contract laboratories, the issues raised above should be addressed. The bottom line is that the AMA is not suitable as a screening tool for endocrine disrupting compounds." [14]

There are many other peer review criticisms of the AMA.[15]

EPA's IQA Guidelines require that EPA ensure that information the Agency disseminates is reproducible and accurate, reliable and unbiased, and it must have utility.[16] In light of the SAP's recent conclusions and recommendations, any EPA information disseminations based on the AMA would violate the IQA Guidelines.

In light of the SAP's recent conclusions and recommendations, any further EPA use of the AMA in the Tier 1 test battery would be arbitrary, capricious and without rational basis.

## III. OMB/OIRA Should Not Approve an EDSP Tier 1 Test Battery which Does Not Include the AMA Because the AMA is "Essential" to the EDSP Tier 1 Test Battery

EPA has repeatedly emphasized that its Tier1 tests have utility only as a complete and complimentary battery of tests, which "was designed to work as a whole":

> "The current EDSP Tier 1 battery consists of 11 diverse yet complementary in vitro and in vivo screening assays as recommended by the FIFRA SAP (SAP, 2008) and is indicated in Table 1. The battery of assays was designed to be conducted as a whole to maximize sensitivity and reliability for determining the potential of a chemical to interact with the E, A, or T hormonal pathways (EDSTAC, 1998)."
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> "The robustness of the Tier 1 battery is based on the strengths of each individual assay and the complementary endpoints within the battery. Thus, '...the value of

[13] Peer Review Report, page 2-1.
[14] Peer Review Report, page 3-17
[15] *E.g.*, Peer Review Report, pages 2-8 to 2-11, 2-14 to 2-15, 2-21 to 2-24, 2-25 to 2-26, 2-27, 2-67 to 2-70, 3-1, 3-7, 3-8, 3-17, 3-25, 3-26, 3-27, 3-31, 3-44, 3-56, to 3-58, 3-59, 3-66, 3-67, 3-69, 3-70, 3-72, 3-80.
[16] EPA IQA Guidelines, pages 15 and 22, available online at http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf .

each individual assay cannot be considered in isolation from other assays in the battery, as they have been combined in a manner such that limitations of one assay are complemented by the strengths of another' (EDSTAC, 1998)."

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"The individual assays that comprise the EDSP Tier 1 battery were designed to be complementary to one another as discussed in Section 2. As a consequence, a more thorough understanding of an E, A, or T endocrine interaction is obtained by the combined analysis of the Tier 1 assays. A fundamental point made throughout this document is that multiple lines of evidence are evaluated in an integrated manner during the WoE [Weight of Evidence] evaluation wherein no one study or endpoint is generally expected to be sufficiently robust to support a decision of whether or not Tier 2 testing is needed." [17]

EPA states that the EDSP Tier 1 "screening battery as proposed is intended to work as a whole":

"The screening battery as proposed is intended to work as a whole….Thus, the robustness of the proposed Tier 1 Screening Battery is based on the strengths of each individual assay and their complementary nature within the battery to detect effects on EAT hormonal function."[18]

EPA has also emphasized to the SAP that the AMA is an "essential" component of the EDSP Tier 1 test battery:

"Thus, this current analysis reinforces the need of both the Amphibian Metamorphosis Assay and the Rat Pubertal assays as essential components of the battery for evaluating the thyroid pathway."

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"[The AMA] is an important assay because amphibian metamorphosis provides a well-studied, thyroid-dependent process which responds to substances known to be active along the HPT axis, and it is the only assay in the EDSP Tier 1 battery that detects thyroid activity in an animal undergoing metamorphosis….[E]ach of the Tier 1 EDSP assays, including the AMA, is intended to be interpreted within a battery of *in vitro* and *in vivo* tests to identify substances with potential to interact with the endocrine system."

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[17] ENDOCRINE DISRUPTOR SCREENING PROGRAM
Weight-of-Evidence: Evaluating Results of EDSP Tier 1 Screening to Identify the Need for Tier 2 Testing, pages 8, 29, 36, available as Document ID EPA-HQ-OPPT-2010-0877-0020 at http://www.regulations.gov.

[18] Page 12, at http://www.epa.gov/scipoly/sap/meetings/2008/march/technical_review.pdf .

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> "[T]he AMA provides useful, complementary, and sometimes unique information about potential perturbations of the HPT axis in amphibians,… conclusions regarding the potential for a test substance to interact with the HPT axis in amphibians and, more broadly, in vertebrate taxa need to be based on a holistic examination of all endpoints in the AMA and within the context of other available data (*i.e.*, the Tier 1 EDSP battery)…."[19]

The AMA should not be used as part of the EDSP Tier 1 test battery. Given the dependence of the entire battery on each included assay, and given that the AMA is "essential" to the battery as a whole, the entire EDSP Tier 1 test battery lacks utility and violates IQA Guidelines and this ICR should not be approved.

We also ask OMB/OIRA to note that, as a failing separate from the AMA problems, the SAP also concluded that the entire Tier1 test battery results so far "suggest that the complementary performance of the multiparameter E [endocrine] battery tests was relatively poor."[20] This is still another reason why the EDSP Tier 1 test battery lacks utility and violates IQA Guidelines. This is still another reason why OMB/OIRA should not approve this ICR.

## IV. OMB/OIRA Should Not Approve this ICR Because the Information Sought Does Not Meet IQA Guideline Requirements and PRA Practical Utility Requirements

In order for OMB to approve this ICR, EPA must demonstrate that all the EDSP Tier 1 test battery will generate information which meets the IQA quality standards of accuracy, reliability, no bias, and utility. EPA cannot make this demonstration for tests that have not been demonstrated to generate accurate, reliable, unbiased and useful information.

OMB's IQA guidance is unambiguous and unequivocal on this requirement:

> "...we note that each agency is already required to demonstrate the 'practical utility' of a proposed collection of information in its PRA submission, i.e., for draft information collections designed to gather information that the agency plans to disseminate. Thus, we think it important that each agency should declare in its guidelines that it will demonstrate in its PRA clearance packages that each such draft information collection will result in information that will be collected,

[19] EPA White Paper for SAP review, pages 12, 110 and 129, Document EPA-HQ-OPP-2013-0075-0003 at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2013-0075-0003 .

[20] SAP Meeting Transcript, page 460, at http://www.epa.gov/scipoly/sap/meetings/2013/may/052113transcript.pdf .

> maintained, and used in a way consistent with the OMB and agency information quality standards. It is important that we make use of the PRA clearance process to help improve the quality of information that agencies collect and disseminate. Thus, OMB will approve only those information collections that are likely to obtain data that will comply with the OMB and agency information quality guidelines."[21]

EPA's own IQA guidelines require EPA to demonstrate to OMB and the public that the EDSP ICR will generate information that complies with the IQA quality standards:

> "For all proposed collections of information that will be disseminated to the public, EPA intends to demonstrate in our Paperwork Reduction Act clearance submissions that the proposed collection of information will result in information that will be collected, maintained and used in ways consistent with the OMB [IQA] guidelines and these EPA [IQA] Guidelines." [22]

Consequently, before OMB can approve this ICR for any EDSP test, EPA has to demonstrate that that test will generate accurate, reliable, unbiased information which has utility. For the reasons stated above, EPA has not made this required demonstration for this ICR, and OMB/OIRA should not approve this ICR.

Independent of the IQA/PRA interface, OMB's ICR rules under the PRA require that EPA demonstrate that these tests will generate accurate, valid, and reliable information which has utility. OMB's ICR rules define the term practical utility as "the actual, not merely the theoretical or potential, usefulness of information to or for an agency, taking into account its accuracy, validity, adequacy, and reliability...."[23]

With regard to EPA's duties, the ICR rules state that "[t]o obtain OMB approval of a collection of information, an agency shall demonstrate that it has taken every reasonable step to ensure that the proposed collection of information...has practical utility."[24]

The PRA itself states:

> "Before approving a proposed collection of information, the Director shall determine whether the collection of information by the agency is necessary for the proper performance of the functions of the agency, including whether the information shall have practical utility."[25]

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[21] Page 12 of OMB IQA Guidance at http://www.whitehouse.gov/sites/default/files/omb/inforeg/iqg_comments.pdf .
[22] *E.g.*, EPA IQA guidelines, Section 6.5, page 28, available online at http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf .
[23] 5 CFR §1320.3(l).
[24] 5 CFR 1320.5(d)(1)(iii).
[25] 44 U.S.C. 3508, at http://www.law.cornell.edu/uscode/text/44/3508 .

With regard to OMB's duties, the ICR rules require that

> "OMB shall determine whether the collection of information, as submitted by the agency, is necessary for the proper performance of the agency's functions. In making this determination, OMB ...will consider whether the burden of the collection of information is justified by its practical utility."[26]

In other words, OMB has an independent, mandatory duty under its own PRA Information Collection rules to determine whether EPA has produced a public record demonstrating that the EDSP Tier 1 test battery covered by this ICR will generate valid, accurate, and useful information. For the reasons stated above, EPA has not produced this required record, and OMB/OIRA should not approve this ICR.

## V. EPA is Abandoning the EDSP Tier 1 Test Battery Covered by this ICR for Faster and More Cost Effective Test Methods

EPA plans to abandon the current Tier 1 tests and proposed Tier 2 tests, and EPA plans to replace them with very different tests. EPA told Congress:

> "In FY2012 EPA will begin a multi-year transition from the [EDSP] to validate and more efficiently use computational toxicology methods and high-throughput assays that will allow the Agency to more quickly and cost-effectively assess potential chemical toxicity."[27]

At EPA's request, another SAP recently reviewed and reported favorably on EPA's development of CompTox methods.[28]

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[26] 5 CFR § 1320.5(e).

[27] See, *e.g.*, U.S. EPA, FY 2012, Justification of Appropriation Estimates for the Committee on appropriations, EPA-190-R-11-003, pages 60-61, http://nepis.epa.gov/Exe/ZyNET.exe/P100A4HZ.TXT?ZyActionD=ZyDocument&Client=EPA&Index=2011+Thru+2015&Docs=&Query=&Time=&EndTime=&SearchMethod=1&TocRestrict=n&Toc=&TocEntry=&QField=&QFieldYear=&QFieldMonth=&QFieldDay=&IntQFieldOp=0&ExtQFieldOp=0&XmlQuery=&File=D%3A%5Czyfiles%5CIndex%20Data%5C11thru15%5CTxt%5C00000002%5CP100A4HZ.txt&User=ANONYMOUS&Password=anonymous&SortMethod=h%7C-&MaximumDocuments=1&FuzzyDegree=0&ImageQuality=r75g8/r75g8/x150y150g16/i425&Display=p%7Cf&DefSeekPage=x&SearchBack=ZyActionL&Back=ZyActionS&BackDesc=Results%20page&MaximumPages=1&ZyEntry=1&SeekPage=x&ZyPURL , quoted in U.S. Environmental Protection Agency Endocrine Disruptor Screening Program Comprehensive Management Plan Comprehensive Management Plan (June 2012), page 6, http://www.epa.gov/endo/pubs/EDSP-comprehensive-management-plan.pdf ; and in Endocrine Disruptor Screening Program for the 21st Century: (EDSP21 Work Plan), page 2, available online at http://www.epa.gov/endo/pubs/edsp21_work_plan_summary%20_overview_final.pdf .

[28] The CompTox SAP's report is available as Document EPA-HQ-OPP-2012-0818-0037 at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0818-0037 .

OMB/OIRA should not approve this ICR for an EDSP Tier 1 test battery which EPA is abandoning for other tests "that will allow the Agency to more quickly and cost-effectively assess potential chemical toxicity." Clearly, EPA has not taken every reasonable step to ensure that the EDSP Tier 1 tests covered by this ICR are the least burdensome necessary, and these tests are not necessary for the proper performance of the functions of the agency.[29]

## VI. Conclusion

OMB/OIRA should not approve this ICR for additional EDSP Tier 1 testing because

- The EDSP Tier 1 test battery includes the AMA, and the SAP recommended that the AMA not be used for additional testing. In EPA's own words, the "recommendations of the Panel from the May FIFRA SAP will be **critical** in how the Agency conducts its weight-of evidence (WoE) evaluation of the Tier 1 screening results…" [30]

- The AMA is "essential" to the test battery as a whole, and the EDSP Tier 1 test battery has no utility as an endocrine disruptor screen without the AMA.

- The SAP identified other failings in the test battery as a whole.

- The EDSP Tier 1 test battery violates IQA Guidelines and the PRA's practical utility requirement because it will not generate accurate, reliable and useful information.

- EPA is abandoning the EDSP Tier 1 test battery for different, faster and more cost-efficient tests. Consequently, the EDSP Tier 1 test battery violates the PRA because it is not the least burdensome tests necessary, and it is not necessary for the proper performance of the functions of the agency.

We thank you for this opportunity to comment.

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[29] See 44 U.S.C. 3508, at http://www.law.cornell.edu/uscode/text/44/3508 ; 5 CFR 1320.5(d), at http://www.law.cornell.edu/cfr/text/5/1320.5 .
[30] Pages 22875-76, at http://www.gpo.gov/fdsys/pkg/FR-2013-04-17/pdf/2013-08921.pdf .